

EXHIBIT 5



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High-dose aspirin in addition to daily low-dose aspirin
decreases platelet activation in patients before and after
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Abstract

Background: Activated platelets play a major role in acute vessel closure after coronary angioplasty. Although aspirin is the routine therapy during angioplasty, it only incompletely prevents acute closure. This might be due to suboptimal dosing. **Objective:** First, to study the effect of additional high-dose aspirin on platelet activation during coronary angioplasty. Second, to assess the potential of the new PFA-100 analyzer to evaluate the effect of different doses of aspirin in patients undergoing angioplasty. **Methods:** Fifty-one patients on 100 mg aspirin/day for at least 1 month were randomized to continuation of 100 mg aspirin/day only (Group A = 24 patients), or to this regime plus a bolus of 1000 mg of aspirin given 1 day before angioplasty (Group B = 27 patients). Results were compared with 15 controls. Platelet function was measured before angioplasty by the PFA-100 analyzer; platelet activation was measured by flow cytometry just before and 1 h after angioplasty. **Results:** At baseline, Group A had significantly more activated platelets than the control group ($P < .001$). High-dose aspirin in Group B resulted in significantly lower platelet activation as compared with both controls ($P < .001$) and Group A ($P < .001$). During angioplasty, the number of activated platelets decreased significantly in Group A ($P < .001$), while there was no change in Group B ($P = .6$). The PFA-100 analyzer was unable to detect differences between the two treatment groups. **Conclusions:** The addition of high-dose aspirin to daily low-dose aspirin, 1 day before coronary angioplasty, significantly reduced the platelet activation state before and after intervention. The PFA-100 analyzer did not detect differences in the effect of low- versus high-dose aspirin on platelet function. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Aspirin; Percutaneous coronary intervention; Human platelets; Flow cytometry; PFA-100 analyzer

1. Introduction

Platelet activation plays a major role in acute vessel closure after percutaneous coronary intervention (PCI). Aspirin pretreatment has been shown to reduce acute closure [1]. However, despite aspirin treatment, coronary thrombosis still

occurs [2,3]. Apparently, platelet inhibition with aspirin only, at dosages currently used, is incomplete.

One reason for aspirin failure during PCI may be that patients become less responsive to fixed long-term dose of aspirin [4]. In vitro studies suggest that an additional anti-thrombotic response can be obtained when aspirin is administered as a high-dose bolus [5]. This better response may be due to inhibition of the prothrombotic effects of erythrocytes on platelet reactivity [5].

These observations made us hypothesize that an increase of aspirin dose may result in a better outcome after PCI. A first step in finding proof for this concept is assessing the effect of additional high-dose aspirin treatment on platelet

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activation in the setting of PCI. For this, we used whole-blood flow cytometry with epitope-dependent monoclonal antibodies, which is an extremely reliable measure of the platelet activation state [6]. However, flow cytometry is labor-intensive and cannot be used as a routine test. Therefore, we also evaluated whether the automated PFA-100 analyzer, which provides results on platelet function within a few minutes, could be a useful alternative to assess the effect of different dosages of aspirin in angioplasty patients.

2. Materials and methods

2.1. Patients

All consecutive patients planned to undergo elective PCI who were on low-dose aspirin for at least 1 month were candidates for enrollment in the trial. Angioplasty for acute myocardial infarction, known allergy to aspirin and use of coumarins, known platelet dysfunction or coagulation disorder, platelet count <90 g/l, hematocrit <0.28 l/l, creatinine >120 $\mu\text{mol/l}$ and planned use of glycoprotein IIb/IIIa receptor blockers were exclusion criteria. In addition, 15 other patients who were on aspirin 100 mg/day for at least 1 month and who underwent diagnostic coronary angiography were studied. This control group served to study the effect of the nonionic, low-osmolality contrast agent (iopromide; Ultravist-370, Schering, Berlin, Germany), used in our clinic, on platelet function and activation.

2.2. Procedures

All study patients continued to use 100 mg of aspirin until after the procedure. Compliance with aspirin treatment was ascertained by a personal interview at the time of randomization, 1 day before and just before intervention. Study patients were randomized 1 week before the intervention to continuation of 100 mg of aspirin only (Group A), or to this regime plus an additional bolus of 1000 mg of aspirin given on the evening before angioplasty (Group B). Randomization was performed by sealed envelopes. All patients gave informed consent and our institutional ethics committee approved the study protocol. The operators and the technician who performed the platelet function studies were blinded for the study medication. The additional high-dose aspirin was given on the evening before angioplasty. Platelet activation was measured just before and 1 h after PCI; PFA-100 measurements were performed just before PCI. At the start of the procedure, a bolus of 70 IU/kg unfractionated heparin was given to all patients. Calcium antagonists were given from the day before the procedure until 6 weeks afterwards. Intravenous nitroglycerin was infused from just before the procedure until 2 h after and 200–500 ml of 0.9% saline was infused during the procedure. A policy of provisional stenting was used. In case of stent placement, clopidogrel was started shortly after the

second blood sample was taken. Electrocardiograms and serum creatine phosphokinase (CPK) and CPK-MB were obtained before and after the procedure. If abnormalities were noted, serial analysis was done.

2.3. Specimen sampling

All blood samples were taken by the same technician after the patient had been supine for at least 30 min, just before and 1 h after angioplasty. Blood was taken from the antecubital vein through a 21-gauge needle with minimal venous congestion. Two milliliters of blood was collected in an EDTA tube for hematocrit determination and platelet count. For determination of factor VIII:c, 2.7 ml of blood was drawn into 0.3 ml of sodium citrate (0.106 M) and placed on ice immediately. Two milliliters of blood was collected in a lithium–heparin tube for measurement of potassium, sodium, creatinine and creatinine phosphokinase. An amount of 4.5 ml of blood was drawn into a Monovette tube (Sarstedt, Nümbrecht, Germany) containing 0.5 ml of 0.105 M buffered sodium citrate (pH 5.5) and kept at room temperature for immediate determination of platelet function and immunolabelling.

2.4. Whole-blood flow cytometry

A no-wash direct double-label immunofluorescence staining procedure in whole blood was used as described previously [6]. The platelet population was identified from its light scatter characteristics and identity was confirmed using a fluorescein isothiocyanate (FITC)-conjugated monoclonal antibody (MAb) to the platelet membrane glycoprotein Ib (25.0 $\mu\text{g/ml}$ CD42a; clone: SZ1; isotype: IgG_{2a}; Beckman Coulter, Mijdrecht, the Netherlands). A bitmap was set around the platelet population and adjusted for each sample in order to ensure that $>98\%$ of the particles analyzed was positive for CD42a. Activated platelets were identified with the use of phycoerythrin (PE)-conjugated MAbs to CD62p (6.25 $\mu\text{g/ml}$) and CD63 (7.5 $\mu\text{g/ml}$) (clones: CLB-Thromb/6 and CLB gran/12, both IgG₁ mouse; Beckman Coulter). CD62p (P-selectin) becomes exposed on the platelet surface coincident with α -granule secretion and CD63 during lysosomal secretion. The IgG₁ mouse control MAb (clone: X40; isotype: IgG₁; Becton Dickinson, Woerden, the Netherlands) was used to set a threshold for activated platelets.

Three microliters whole blood was diluted with 30 μl of Isoton II (Beckman Coulter) and incubated with 2 μl of saturating concentrations of antibodies for 25 min in darkness. After the incubation procedure, the mixture was diluted with 1 ml of 1% paraformaldehyde in Isoton II and analyzed on an EPICS II flow cytometer (Beckman Coulter). Ten thousand platelets were counted and activation state was expressed as the absolute number of platelets positive for a specific epitope using XL2 software after the subtraction of nonspecific binding of MAbs.

2.5. Platelet function testing

The PFA-100 analyzer (Dade Behring, Germany) was used, which measures the platelet-related primary hemostasis capacity of anticoagulated whole blood under high shear conditions. The time needed to form a platelet plug occluding the aperture cut into a collagen/epinephrine (COL/EPI)- or collagen/adenosine 5'-diphosphate (COL/ADP)-coated membrane is determined and reported as the closure time (CT). The combination of the two tests enables discrimination of aspirin effects from other causes of platelet dysfunction [7]. Reference values [10–90 percentiles] established in our laboratory were 79–142 s for COL/EPI (CV 11.5%) and 60–100 s for COL/ADP (CV 9.6%)-induced CT. Based on the COL/EPI results, patients were categorized as nonresponders (CT < 142 s), less-responders (142 ≤ CT ≤ 300 s) or responders (CT > 300 s).

2.6. Factor VIII:c assay

Factor VIII:c analysis was done on the STA-R (Boehringer, Mannheim, Germany) according to the standard procedure with Roche reagent PTT^a. Normal values for factor VIII:c are 80–160%.

2.7. Statistical analysis

Differences in treatment groups were tested with Student's *t* test or with the nonparametric Wilcoxon's rank sum test. Results are reported as mean (standard deviation), respectively, as median [25–75 percentiles]. Platelet count was adjusted for hemodilution according to van Beaumont [8].

3. Results

Randomization assigned 24 patients to Group A (100 mg of aspirin) and 27 patients to Group B (100+1000 mg of aspirin). The basic clinical and angiographic characteristics did not differ significantly between the two groups (Table 1). A stent was placed in 11 patients (44%) in Group A and in 13 patients (48%) in Group B. Angioplasty was complicated in one patient in Group A, who developed a non Q-wave myocardial infarction due to side branch occlusion. None of the patients suffered from a bleeding complication.

3.1. Control group

In two controls, obstructive coronary disease (lesion >50% diameter stenosis) was diagnosed. Average values for hematocrit and platelet count are depicted in Table 2. Angiography resulted in a nonsignificant increase in the median indexes for CD62p and CD63 (Table 2). The median COL/EPI-induced CT was 300 (238–300) s; the median COL/ADP-induced CT was 88 (84–119) s. Nine control patients showed normal COL/EPI-induced aggregation val-

Table 1
Clinical and angiographic characteristics of the study patients

	Group A (n=24)	Group B (n=27)	P value
Age (years)	63.8 ± 1.8	65.2 ± 12.0	.7
Male sex	21 (88)	22 (82)	.7
Risk factors			
Diabetes	2 (8)	1 (4)	.3
Hypertension	7 (29)	9 (33)	.8
Total cholesterol > 5 mmol/l	18 (75)	22 (81)	.7
Smoking in preceding half year	6 (25)	5 (19)	.7
Clinical history			
Previous myocardial infarction	10 (42)	6 (22)	.2
Previous angioplasty	40 (15)	37 (14)	.3
Angina class (CCS ^a)			
I	1 (4)	2 (7)	
II	13 (54)	8 (30)	
III	10 (42)	17 (63)	.3
β-blocker use	20 (83)	22 (82)	1.0
Statin use	12 (50)	12 (44)	.8
Ejection fraction < 50%	5 (21)	4 (15)	.9
Number of diseased vessels			
1	17 (71)	22 (82)	
2	6 (25)	3 (11)	
3	1 (4)	1 (4)	.5
Lesion type			
A/B1	11 (48)	14 (45)	
B2/C	18 (62)	17 (55)	.6
Reference diameter	3.11 ± 0.45	3.27 ± 0.40	.2
Stented lesions	11 (46)	13 (48)	1.0

Age is expressed as mean ± SD; the other values are expressed as numbers (%).

^a The Canadian Society Cardiovascular classification was used.

ues, five patients were less-responders and one patient was a nonresponder. The mean ± SD for factor VIII:c was 132 ± 35%.

3.2. Hemocytometric data and platelet activation before intervention in Groups A and B

Average values for hematocrit and platelet count were similar in the two study groups (Table 2). Mean ± SD for factor VIII:c were also similar in the two groups (153 ± 43% in Group A and 157 ± 39% in Group B, *P* = NS). The factor VIII:c values in Groups A and B did not differ significantly from controls (*P* = .32 and *P* = .16, respectively).

Median indexes for CD62p and CD63 in Group A were significantly higher than in controls (Table 2). Median indexes for CD62p in Group B, however, were significantly lower than both in controls and Group A. CD63 value in Group B was significantly lower than in Group A, and similar to that in the control group (Table 2).

3.3. Hemocytometric data and platelet activation after intervention in Groups A and B

During intervention, the hematocrit decreased significantly in both Groups A and B (Table 2). Also the platelet count decreased during intervention in the two groups, but

Table 2
Data on hemocytometry, platelet activation and platelet function of controls and Groups A and B

	n	Hematocrit	Thrombocyte	Thrombocyte corrected	CD62p-positive platelets per 10,000 platelets	CD63-positive platelets per 10,000 platelets	COL/EP1-induced CT	Nonresponders	Less-responders	Responders
Controls	15									
Before CAG		0.41 (0.02)	204 (52)		18	14-24	0	0-0	100	238-300
After CAG		0.40 (0.02)	202 (52)	214 (61)	29	15-39	8	2-11		
P		.04	NS	NS	NS		NS			
Group A	24									
Before PCI		0.41 (0.03)	209 (42)		69*	28-172	18*	8-37	>300	156-300
After PCI		0.39 (0.04)	202 (42)	224 (49)	24	8-56	7	0-18		
P		.002	NS	NS	<.001		.03			
Group B	27									
Before PCI		0.41 (0.04)	244 (85)		0*	0-6	0	0-0	202	135-300
After PCI		0.39 (0.04)	234 (84)	263 (107)	0	0-0	0	0-0		
P		.04	NS	NS	NS		NS			
P, Group A vs. Group B					<.001		<.001			
Before PCI										
P, Group A vs. Group B					<.001		.003			
After PCI										

Group A = 100 mg of aspirin; Group B = 100 + 1000 mg of aspirin; CAG = coronary angiography. Nonresponder (CT < normal); less-responder (142 ≤ CT ≤ 300 s); responder (CT > 300 s).

* Statistical significance of Group A or B vs. controls. Statistical significance P < .05.

when corrected for hematocrit, this number appeared to be increased in both groups (Table 2).

The median CD62p index decreased significantly in Group A, whilst CD62p remained almost undetectable in Group B (Table 2). Findings with CD63 assessment were similar: a significant decrease was noted in Group A, whilst undetectable pre and post in Group B (Table 2).

3.4. Platelet function before intervention in Groups A and B

Before intervention, only 13/24 (54%) patients in Group A and 16/27 (59%) patients in Group B showed a full response to aspirin ($P=0.7$) (Table 2). Thus, many patients in both groups were less- or nonresponders to aspirin. In addition, high-dose aspirin did not significantly prolong the COL/EPI-induced CT (Table 2). The median COL/ADP-induced CT was within the normal range in both groups (data not shown).

3.5. Correlation between platelet activation and CT

There was no correlation between values for platelet activation and factor VIII:c, neither between values for platelet activation and COL/EPI-induced CT.

3.6. Balloon versus stent

Before and after angioplasty, no significant difference was noted in platelet activation state between stented and non-stented patients both for Groups A and B (data not shown).

4. Discussion

The dosage of aspirin required for complete inhibition of platelet aggregation varies for each subject [9–11]. Furthermore, the inhibitory effect of a fixed dose of aspirin might decrease over time [4]. Therefore, less-responders to long-term low-dose aspirin may benefit from an additional high-dose aspirin to prevent platelet aggregation during coronary intervention. Our results show that administration of a high-dose bolus of aspirin in addition to long-term, low-dose aspirin significantly reduces platelet activation before and during intervention. This suggests that additional high-dose aspirin may prevent peri-interventional complications because high platelet activation has been shown to be associated with an increased risk of coronary thrombosis during coronary angioplasty [12].

4.1. Platelet activation

In the present study, three interesting observations related to platelet activation were made. First, in patients with symptomatic coronary disease, long-term treatment with low-dose aspirin did not prevent an activated platelet state. This was demonstrated by more activated platelets in Group A as compared with the control group. Thus, platelet inhibition

with long-term 100 mg/day aspirin is incomplete. Second, an additional bolus of 1000 mg of aspirin 1 day prior to intervention almost completely eliminated platelet activation. The number of activated platelets in Group B was even less than in the control group. Third, in patients pretreated with low-dose aspirin only, the number of activated platelets decreased during intervention, whereas platelet activation remained constant in patients treated with a high-dose bolus aspirin. This decrease of activated platelets could have been due to consumption, as has been demonstrated before [13]. We can only speculate that part of these platelets was attached to the activated plaque. In contrast, platelet activation increased in the control group due to the angiography and/or contrast agent, as has been demonstrated previously [14]. These controls, however, did not have an angioplasty-damaged vessel wall serving as a substrate for platelet attachment. In the treatment groups, the total platelet count showed an increase, which was probably due to recruitment of originally sedentary platelets from the spleen, bone marrow and lungs [15].

4.2. PFA-100 analyzer

Our data demonstrate that in patients undergoing PCI who are on low-dose aspirin, the present PFA-100 system is unable to detect the effect of additional high-dose aspirin. The poor sensitivity of the present PFA-100 system may be due to the high concentrations of stimuli in the COL/EPI cartridge [16]. These powerful thrombotic stimuli could bypass the arachidonic acid pathway leading directly to platelet activation. An additional reason may be the limitation of the CT to 300 s.

In contrast, the PFA-100 system may be useful to detect non- or less-responders. In our study, many patients were non- or less-responders to long-term aspirin. This is in agreement with previous observations, showing that only about half of the patients with atherosclerosis shows the expected effect of aspirin [4,17–19]. Less-responders to aspirin may be at higher risk for thrombotic complications during angioplasty and may therefore benefit from the use of stronger antithrombotics such as the platelet glycoprotein IIb/IIIa receptor blockers. Likewise, Mueller et al. [18] demonstrated that reocclusion following peripheral arterial angioplasty could be predicted based on insufficient response to aspirin with use of whole-blood aggregometry. However, we have to stress that prospective trials are required to prove clinical benefit for patients in terms of event-free survival after PCI and the predictive value of the PFA-100 for the outcome.

Because platelet-related primary hemostasis under high shear conditions depends on von Willebrand factor levels, we also measured factor VIII:c activity, which is closely linked to von Willebrand factor [15]. In contrast to others, we did not find a correlation between factor VIII:c activity and COL/EPI-induced CTs [20]. Therefore, in our study, differences in von Willebrand factor cannot be the explanation.

ation for the observed differences between responders and less- or nonresponders.

4.3. Limitations

Because most patients undergoing angioplasty in our center are referred from other centers, we were unable to measure the platelet activation status before the administration of a high-dose bolus of aspirin in Group B. Thus, we do not know the direct effect of high-dose aspirin on the platelet activation status. However, considering that the administration of an additional dose of aspirin was the only major difference between the two study groups, it is reasonable to conclude that the reduced activation status in Group B was due to the high-dose aspirin.

5. Conclusion

An additional bolus of 1000 mg of aspirin given 1 day before coronary angioplasty almost completely abolishes platelet activation before and after coronary intervention, while 100 mg of aspirin per day only does not. In addition, in patients undergoing PCI who are on low-dose aspirin, the present PFA-100 system is unable to detect the effect of additional high-dose aspirin.

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